

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Romero Confirmation No. 5228
Serial No.: 10/782,245 Examiner: Hasan Syed Ahmed
Filing Date: 02/18/2004 Group Art Unit: 1615

DECLARATION UNDER 37 CFR § 1.132 IN SUPPORT OF NON-OBVIOUSNESS

I, Dr. Manesh Dixit, do hereby declare the following:

1. I hold a PhD. in Pharmaceutics from The Ohio State University in Columbus Ohio.
2. I am a Registered Patent Agent with the United States Patent and Trademark Office, Registration No. 55,784.
3. I am currently Executive Vice President, Research and Development for Nostrum Pharmaceuticals, Inc. in Edison N.J.
4. I had previously worked as a Senior Patent Agent for Ivax, Corp. in Miami FL.
5. Prior to my work as a Patent Agent, I was a Senior Principal Scientist at Andrx Pharmaceuticals working with solid oral controlled release products including issues relating to patentable formulations, biopharmaceutics, preformulation, formulation, and scale-up.
6. My work at Andrx in the field of pharmaceutical formulations was more than five years.
7. I am a coinventor of four pending patent applications in the field of controlled release dosage forms. The following three applications have been published:

- a. M. Dixit, C. Chen, X. Cheng, and J. Xie, "Oral controlled release dosage forms", US2004/0156896 A1.
- b. M. Dixit, X. Cheng, A. Nangia and C. Chen, "Extended release Venlafaxine formulation", US2005/0106248 A1.
- c. X. Cheng, X. Qi, G. Zhang and M. Dixit, "Diltiazem controlled release formulation and method of manufacture", US 2007/0036856 A1.

8. I have authored or co authored the following papers and ABSTRACTS:

- a. Dixit, M.A. and Frank, S.G., "An efficient gel formulation for iontophoresis", *13th Annual Meeting, AAPS*, San Francisco, CA, November, 1998.
- b. Dixit, M.A. and Frank, S.G., "Liquid crystalline phases as donor media for iontophoresis", *13th Annual Meeting, AAPS*, San Francisco, CA, November, 1998.
- c. Dixit, M.A. and Frank, S.G., "Iontophoretic drug release from lyotropic liquid crystalline formulations", *25th International Symposium on Controlled Release of Bioactive Materials*, Las Vegas, NV, June, 1998.
- d. Dixit, M.A. and Frank, S.G., "Iontophoresis from liquid crystalline formulations", *12th Annual Meeting, AAPS*, Boston, MA, November, 1997.
- e. Frank, S.G., Chen, Wen-Hsia and Dixit, M.A., "Effect of current density, drug concentration and operating conditions in a novel *in vitro* system for iontophoresis", *Symposium on Transdermal Administration a Case study, Iontophoresis, APGI/CRS*, Paris, March, 1997.

9. The process of discerning aspects of pharmaceutical formulations including issues relating to pharmaceutics, pharmacokinetics, and patents, has been an integral part of my career for more than eight years.

10. My current position with Nostrum Pharmaceuticals involves the same responsibilities as enumerated above.

11. I am familiar with the disclosure, subject matter, and currently pending claims of US Patent Application No. 10/782,245.
12. I have further reviewed US Patent Nos. 6,210,710; 5,252,339; and US Patent Application Publication No. 2005/0008690; each of which is cited in the Office Action mailed August 27, 2007.
13. I have also reviewed the rejection of the currently pending claims in the Office Action mailed August 27, 2007 based on obviousness over the cited references.
14. Based on the facts set forth below, it is my professional opinion that a person having ordinary skill in the art of solid dosage formulations would not combine the cited references in the manner described in the Office Action mailed August 27, 2007 in the subject application.
15. The Office Action, on page 4, quotes the Skinner reference and states: "Skinner explains that the disclosed composition is beneficial because it provides flexibility in release profiles that are stable and economical for compressed tablets." (emphasis added).
16. The formulations claimed in the subject application relate to coated pellets and are not directed to compressed tablets.
17. I understand and set forth that there are a large number of formulation variables and considerations that are completely different when preparing compressed tablet formulations as opposed to layered pelletized formulations.
18. Compressed tablet formulations, whether they are direct compression, granulation, or any other compressible form, require formulation considerations relating to tablet compression material blend uniformity, compressed tablet content uniformity, flowability of tablet compression material blend, compressibility of tablet compression material blend, and tablet friability of compressed tablets.
19. Coated pellets require formulation considerations relating to a completely different set of parameters.

20. Coated pellets require formulation considerations relating to percentage and active ingredient loading per pellet, pellet size, particle size of active components, and particle size of excipients.
21. Functional coatings, i.e. controlled release, delayed release, sustained release and the like, require attention to different parameters when coating pellets as opposed to coating compressed tablets.
22. Because solid dosage formulation science encompasses a large amount of active ingredients and excipients, suitable percentages for a particular formulation are not attainable through routine or manipulative experimentation as characterized on page 4 of the Office Action.
23. I further recognize "it is not inventive to discover the optimum or workable ranges by routine experimentation" as set forth on page 4 of the office action. However, to the vast array of the formulation of variables present when preparing any solid dosage form in general, and the pellets of the claimed invention in particular, it is my opinion that the instant percentage ranges provided an unexpected result relating to the release characteristics set forth in the pending claims.
24. As set forth in paragraphs 15 through 22 above, and further in view of the office action characterization on the fourth paragraph of page for that the release profile of the instant claims 23 and 51 may be determined by a person of ordinary skill in the art based on routine experimentation, this characterization is incorrect. There are thousands of active ingredients placed in dosage forms and there are thousands of known excipients to be combined with the active ingredients. Although certain aspects of active ingredients and excipients are known, their interactions based on combination and percentage composition are uncertain.
25. The difficulties of formulating consistent, stable, and effective layered pellets is increased greatly as the load on the pellets increases. The pellets claimed in the subject application are loaded with active plus excipients in the range of 65-98.5% w/w. Loaded pellets at these levels are extremely difficult to

formulate and percentages of active and excipients are crucial to produce consistent and stable layered pellets.

26. Also based on the facts and Exhibits set forth below, it is my professional opinion that there is evidence of a long-felt yet unmet need for the formulation described in the subject application.
27. Also based on the facts and Exhibits set forth below, it is further my professional opinion that other products have failed to address the need for the invention in the subject application.
28. Information available from a National Institutes of Health (NIH) study, (attached as Exhibit A) available at <http://nccam.nih.gov/research/results/gait/qa.htm#c3> indicate dosage at Glucosamine alone: 1500 mg daily given as 500 mg three times a day Chondroitin sulfate alone: 1200 mg daily given as 400 mg three times a day Glucosamine plus chondroitin sulfate combined: same doses-1500 mg and 1200 mg daily and further indicate "side effects were mild, such as upset stomach, and were spread evenly across the different treatment groups."
29. It is my professional opinion that controlled release formulations, prepared according to the claimed invention can provide therapy at reduced dosage levels than those in the NIH study, which would in turn reduce the gastric incidents reported in the NIH study. This is because elevated dosage levels are required to account for first pass hepatic elimination and the water soluble nature of the actives provided as immediate release dosage forms.
30. Based on my nearly 10 years experience in the field solid dosage formulations, I strongly believe the invention in the subject patent application will have a high likelihood of commercial success
31. As states in item 12 above, I have reviewed US Patent Nos. 6,210,710; 5,252,339; and US Patent Application Publication No. 2005/0008690; each of which is cited in the Office Action mailed August 27, 2007 as well as the Office Action itself in which the claimed invention is rejected as being an obvious combination of the cited references.

32. US Patent Nos. 6,210,710 and 5,252,339 have disclosure only applicable to formulations for compressed tablets.
33. US Patent Application Publication No. 2005/0008690 is for a very complex multi phase/multi compartment dosage form.
34. I do not believe that it would be obvious to a person having ordinary skill and knowledge in solid dosage formulations to combine the disclosures in the manner set forth in the Office Action and reach the subject invention as now claimed. When comparing the aforementioned patents with the differences of the invention claimed in the subject application, it is my opinion that persons in the art would neither look to formulations for compressed tablets to arrive at a formulation to be used in layered pellets, nor would they combine the multi compartment disclosure with compressed tablet formulations to arrive at the invention as claimed in the subject application.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-reference application or any patent issuing thereon.

MD Dixit

Manesh A. Dixit, PhD.

Date: Nov. 26th, 2007

EXHIBIT A

BACK GROUNDER

NATIONAL CENTER FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE

Questions and Answers: NIH Glucosamine/chondroitin Arthritis Intervention Trial (GAIT)

About the Study

What is the Glucosamine/chondroitin Arthritis Intervention Trial (GAIT)?

GAIT is the first large-scale, multicenter clinical trial in the United States to test the effects of the dietary supplements glucosamine hydrochloride (glucosamine) and sodium chondroitin sulfate (chondroitin sulfate) for the treatment of knee osteoarthritis. The study tested whether glucosamine and chondroitin sulfate used separately or in combination reduced pain in participants with knee osteoarthritis.

The University of Utah, School of Medicine coordinated this study, which was conducted at 16 rheumatology research centers across the United States. The National Center for Complementary and Alternative Medicine (NCCAM) and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), two components of the National Institutes of Health (NIH), funded GAIT.

What was the purpose of the study?

Previous studies in the medical literature had conflicting results on the effectiveness of glucosamine and chondroitin sulfate as treatments for osteoarthritis. GAIT was designed to test the short-term (6 months) effectiveness of glucosamine and chondroitin sulfate in reducing pain in a large number of participants with knee osteoarthritis.

What was the basic design of the study?

In GAIT, participants were randomly assigned to one of five treatment groups: (1) glucosamine alone, (2) chondroitin sulfate alone, (3) glucosamine and chondroitin sulfate in combination, (4) celecoxib, or (5) a placebo (an inactive substance that looks like the study substance). Glucosamine and chondroitin sulfate and their combination were compared with a placebo to evaluate whether these substances significantly improve joint pain. Celecoxib, which is a prescription drug effective in managing osteoarthritis pain, was also compared with placebo to validate the study design.

To reduce the chance of biased results, the study was double-blinded—neither the researchers nor the participants knew which of the five treatment groups the participants were in. Participants received treatment for 24 weeks. Participants were evaluated at the start of the study and at weeks 4, 8, 16, and 24 and closely monitored for improvement of their symptoms as well as for any possible adverse reactions to the study agents. X-rays documented each participant's diagnosis of osteoarthritis. Participants were also stratified into two pain subgroups—1,229 participants (78 percent) with mild pain and 354 participants (22 percent) with moderate-to-severe pain.

A positive response to treatment was defined as a 20 percent or greater reduction in pain at week 24 compared with the start of the study. All participants had the option to use up to 4,000 mg of acetaminophen, as needed, to control pain from osteoarthritis throughout the study, except for the 24 hours prior to having their knee assessed. Acetaminophen use was low: on average, participants used fewer than two 500 mg tablets per day.

What did GAIT cost?

The primary GAIT study cost just over \$12.5 million.

Study Background

What is osteoarthritis?

More than 20 million adults in the United States live with osteoarthritis—the most common type of arthritis. Osteoarthritis, also called degenerative joint disease, is caused by the breakdown of cartilage, which is the connective tissue that cushions the ends of bones within the joint. Osteoarthritis is characterized by pain, joint damage, and limited motion. The disease generally occurs late in life and most commonly affects the hands and large weight-bearing joints, such as the knees. Age, female gender, and obesity are risk factors for this condition.

What are glucosamine and chondroitin sulfate?

Glucosamine and chondroitin sulfate are natural substances found in and around the cells of cartilage. Glucosamine is an amino sugar that the body produces and distributes in cartilage and other connective tissue, and chondroitin sulfate is a complex carbohydrate that helps cartilage retain water. In the United States, glucosamine and chondroitin sulfate are sold as dietary supplements, which are regulated as foods rather than drugs.

What is celecoxib?

Celecoxib (brand name Celebrex) is a type of nonsteroidal anti-inflammatory drug (NSAID), called a COX-2 inhibitor. Like traditional NSAIDs, celecoxib blocks the COX-2 enzyme in the body that stimulates inflammation. Unlike traditional NSAIDs, however, celecoxib does not block the action of COX-1 enzyme, which is known to protect the stomach lining. As a result, celecoxib reduces joint pain and inflammation with reduced risk of gastrointestinal ulceration and bleeding. Recent reports have linked possible cardiovascular side effects to COX-2 inhibitors. Although GAIT was not designed to study the safety of celecoxib, participants were monitored for adverse events and no increase in such side effects was observed.

What doses were used for the various treatments?

The doses used in GAIT were based on the doses seen in the prevailing scientific literature.

- Glucosamine alone: 1,500 mg daily, given as 500 mg three times a day
- Chondroitin sulfate alone: 1,200 mg daily, given as 400 mg three times a day
- Glucosamine plus chondroitin sulfate combined: same doses—1,500 mg and 1,200 mg daily
- Celecoxib: 200 mg daily
- Acetaminophen: participants were allowed to take up to 4,000 mg (500 mg tablets) per day to control pain, except for the 24 hours before pain was assessed.

Who provided the source materials for making the glucosamine and chondroitin sulfate products used in GAIT?

- Glucosamine was donated in part by Ferro Pfanstiehl Laboratories, Inc., Waukegan, IL, through Wilke Resources.
- Chondroitin sulfate was donated by Bioiberica, S.A., Barcelona, Spain.

The study agents were manufactured by the Albuquerque Veterans Affairs (VA) Cooperative Studies Program Clinical Research Pharmacy.

Where did the other study products come from?

- Acetaminophen was donated by McNeil Consumer and Specialty Pharmaceuticals, Fort Washington, PA.
- Celecoxib was purchased from Pfizer.

Where was the study conducted?

The University of Utah, School of Medicine, Salt Lake City, UT, served as the coordinating study center and oversaw the research and recruitment efforts of the 16 study centers. The study was led by Daniel O. Clegg, M.D., a Professor of Medicine and Chief of Rheumatology, Division of Rheumatology, University of Utah, School of Medicine. The GAIT biostatistician was Domenic J. Reda, Ph.D., from the Hines VA Cooperative Studies Program, which served as the study data management and analysis center. The GAIT Clinical Research Pharmacist was Crystal L. Harris, Pharm.D., at the Albuquerque VA Cooperative Studies Program Clinical Research Pharmacy, which manufactured, packaged, distributed, and provided analytical testing of the study agents along with regulatory support for GAIT. The 16 study centers and their lead investigators were:

- University of Alabama at Birmingham, Birmingham, AL; Larry W. Moreland, M.D.
- University of Arizona, Tucson, AZ; David Yocum, M.D.
- Cedars-Sinai Medical Center, Los Angeles, CA; Michael Weisman, M.D.
- University of California Los Angeles, Los Angeles, CA; Daniel Furst, M.D.
- University of California San Francisco, San Francisco, CA; Nancy Lane, M.D.
- Northwestern University, Chicago, IL; Thomas J. Schnitzer, M.D.
- Indiana University, Indianapolis, IN; John Bradley, M.D.
- The Arthritis Research and Clinical Centers, Wichita, KS; Frederick Wolfe, M.D.
- University of Nebraska Medical Center, Omaha, NE; James O'Dell, M.D.
- Hospital for Joint Diseases, New York, NY; Clifton Bingham, III, M.D.

- Case Western Reserve University, Cleveland, OH; Michele Hooper, M.D.
- University of Pennsylvania, Philadelphia, PA; H. Ralph Schumacher, Jr., M.D.
- University of Pittsburgh, Pittsburgh, PA; Chester Oddis, M.D.
- Presbyterian Hospital of Dallas, Dallas, TX; John J. Cush, M.D.
- University of Utah, Salt Lake City, UT; Christopher G. Jackson, M.D.
- Virginia Mason Medical Center, Seattle, WA; Jerry Molitor, M.D.

Key Results

What were the key results of the study?

Researchers found that:

- Participants taking the positive control, celecoxib, experienced statistically significant pain relief versus placebo—about 70 percent of those taking celecoxib had a 20 percent or greater reduction in pain versus about 60 percent for placebo.
- Overall, there were no significant differences between the other treatments tested and placebo.
- For a subset of participants with moderate-to-severe pain, glucosamine combined with chondroitin sulfate provided statistically significant pain relief compared with placebo—about 79 percent had a 20 percent or greater reduction in pain versus about 54 percent for placebo. According to the researchers, because of the small size of this subgroup these findings should be considered preliminary and need to be confirmed in further studies.
- For participants in the mild pain subset, glucosamine and chondroitin sulfate together or alone did not provide statistically significant pain relief.

How many people participated in the study and who were they?

A total of 1,583 people participated in the study. People age 40 or older with knee pain and documented x-ray evidence of osteoarthritis were eligible to participate. Participants could not have used glucosamine for 3 months and chondroitin sulfate for 6 months prior to entering the study. Participants were about 59 years of age, on average, and nearly two-thirds of participants were women. Of the 1,583 study participants, 78 percent (1,229) were in the mild pain subgroup and 22 percent (354) were in the moderate-to-severe pain subgroup.

Were there any side effects from the treatments?

There were 77 reports of serious adverse effects during the study. Of those 77, only 3 were attributed to study treatments. Most side effects were mild, such as upset stomach, and were spread evenly across the different treatment groups. In addition, although GAIT was not designed to evaluate these risks, no change in glucose tolerance was seen for glucosamine nor was an increased incidence of cardiovascular events seen with celecoxib.

Consumer Information and Next Steps

Should people with osteoarthritis use glucosamine and chondroitin sulfate?

People with osteoarthritis should work with their health care provider to develop a comprehensive plan for managing their arthritis pain: eat right, exercise, lose excess weight, and use proven pain medications. If people have moderate-to-severe pain, they should talk with their health care provider about whether glucosamine plus chondroitin sulfate is an appropriate treatment option.

Can U.S. consumers get the glucosamine and chondroitin sulfate products used in GAIT?

Identical products may not be commercially available. GAIT was conducted under an Investigational New Drug application filed with the U.S. Food and Drug Administration (FDA). All of the products used in the study were developed for the study and subject to the FDA's pharmaceutical regulations. The products were evaluated and manufactured by the VA Cooperative Studies Program Clinical Research Pharmacy, an FDA-licensed clinical research pharmacy center. The glucosamine and chondroitin sulfate used were tested for purity, potency, quality, and consistency among batches. Products were retested for stability throughout the study.

Will the GAIT team continue to do research on glucosamine and chondroitin sulfate?

GAIT includes an ancillary study, which is still ongoing, that will assess whether glucosamine and chondroitin sulfate can reduce or halt the progression of knee osteoarthritis following additional treatment. About one-half of the participants enrolled in GAIT will be treated for an additional 18 months. As in the primary study, participants will not know to which treatment group they belong. Researchers will compare x-rays taken at the beginning of the study and after 1 and 2 years of treatment to identify changes in the knee joints as a result of treatment. Results are expected in late 2007 or early 2008.

For More Information

NCCAM Clearinghouse

The NCCAM Clearinghouse provides information on complementary and alternative medicine (CAM) and NCCAM, including publications and searches of Federal databases of scientific and medical literature. The Clearinghouse does not provide medical advice, treatment recommendations, or referrals to practitioners.

Toll-free in the U.S.: 1-888-644-6226

TTY (for deaf and hard-of-hearing callers): 1-866-464-3615

Web site: nccam.nih.gov

E-mail: info@nccam.nih.gov

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), NIH

NIAMS supports research into the causes, treatment, and prevention of arthritis and musculoskeletal and skin diseases; the training of scientists; and the sharing of research-based information.

Web site: www.niams.nih.gov

Toll-free in the U.S.: 1-877-22-NIAMS

Office of Dietary Supplements (ODS), NIH

ODS seeks to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, supporting research, sharing research results, and educating the public. Its resources include publications and the International Bibliographic Information on Dietary Supplements database.

Web site: www.ods.od.nih.gov

E-mail: ods@nih.gov

U.S. Food and Drug Administration (FDA)

The FDA oversees the safety of many products, such as foods (including dietary supplements), medicines, medical devices, and cosmetics.

Web site: www.fda.gov

Toll-free in the U.S.: 1-888-463-6332

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